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The Effect of the Clinical Digital Rectal Exam on the Complexed Prostate-Specific Antigen Versus the Total Prostate-Specific Antigen

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The Effect of the Clinical Digital Rectal Exam on the Complexed Prostate-Specific Antigen Versus the Total Prostate-Specific Antigen

Abstract

Background: The total serum prostate-specific antigen has been used as a screening tool to determine prostate health and is routinely done after a clinical exam which may include a digital rectal exam. The complexed prostate-specific antigen is a portion of the total prostate-specific antigen and may be a better indicator for prostate health. The purpose of this paper is to evaluate the effect that the digital rectal exam has on both the total prostate-specific antigen and the complexed prostate-specific antigen. The evidence will be evaluated using the GRADE system.

Method: An exhaustive search of available medical literature was conducted using Medline, Web of Science, Cochrane Systematic Reviews and CINAHL.

Results: There were four studies included in the review. The change in total and complexed prostate-specific antigen serum values in ng/mL post digital rectal examination was evaluated across the studies. Due to the fact that the complexed prostate-specific antigen is a subset of the total prostate-specific antigen the consequences of the digital rectal examination was compared using a percent change.

Conclusion: The complexed prostate-specific antigen is affected less by the digital rectal exam and would indicate that it may be a more reliable marker for prostate health compared to the total prostate-specific antigen. This recommendation needs to be used with caution as the overall GRADE of evidence was considered low and additional research is likely to have an impact on the confidence of the recommendation[TC1].

[TC1]No references are included in the abstract.

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PSA, prostate-specific antigen, digital rectal exam, DRE, massage, manipulation

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The Effect of the Clinical Digital Rectal Exam on the Complexed Prostate-Specific Antigen Versus the Total Prostate-Specific Antigen

Jason Brown



A course paper presented to the College of Health Professions
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Biography

Jason Brown is a native of Vancouver, Washington where he majored in Biology at Washington State University. Prior to completing his degree, he spent six years in the United States Air Force where he worked as a communications computer systems operator and a medical technician. After serving his time he spent the next seven years of his life working at a semiconductor manufacturing company prior to returning to school.

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To Leslie Brown: Thank you for your continued support and being the person and wife you are. There are not enough words to describe how lucky I am to have you as my partner in life's journey. You are the best and I love you very much.

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To my family: Thank you for your patience throughout my journey. From sending me off with home cooked meals to a call from home it was always nice to have your love, encouragement and understanding.

ABSTRACT

Background: The total serum prostate-specific antigen has been used as a screening tool to determine prostate health and is routinely done after a clinical exam which may include a digital rectal exam. The complexed prostate-specific antigen is a portion of the total prostate-specific antigen and may be a better indicator for prostate health. The purpose of this paper is to evaluate the effect that the digital rectal exam has on both the total prostate-specific antigen and the complexed prostate-specific antigen. The evidence will be evaluated using the GRADE system.

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Keywords: Manipulation, massage, prostate-specific antigen, PSA, digital rectal examination, DRE

TABLE OF CONTENTS

INTRODUCTION	5
Background	5
Purpose of the Study	6
METHOD	6
RESULTS	7
DISCUSSION.....	9
REFERENCES	16
APPENDIXES.....	17
A. Table 1: GRADE	18
B. Figure 1: Percent change in PSA levels after DRE	19

INTRODUCTION

Background

The American Cancer Society (ACS, 2010) reports prostate cancer to be the second leading cause of death in males behind lung cancer and that one out of six males will be diagnosed with prostate cancer during their lifetime. They also report that 217,730 cases of prostate cancer were diagnosed in 2010 and that one out of 36 males will eventually die from prostate cancer.

The United States Preventive Services Task Force (USPSTF) does not currently recommend regular prostate screening and the ACS recommends routine screening beginning at the age of 50 in healthy adult males. If there is an increased risk of prostate cancer, the ACS recommends screening to begin as soon as 40 (USPSTF, 2008 & American Cancer Society, 2010).

The digital rectal exam (DRE) used in conjunction with the prostate-specific antigen (PSA) continue to be the most widely used screening tool to evaluate disorders of the prostate including cancer. However, the sensitivity and specificity of the PSA screening test is approximately 20 to 40 percent so it is not the ideal test that is used for a tumor marker (Fischbach & Dunning, 2009). The PSA is a glycoprotein. When referring to PSA the total prostate-specific antigen (tPSA) is what is actually being measured and there are multiple components that comprise the tPSA. Of those components, approximately 65-95% is bound to 1-antichymotrypsin (ACT), as complexed prostate-specific antigen (cPSA). The complexed form is made up of other types including 1-protease inhibitor, and 2-macroglobulin, protein C inhibitor, inter 1-trypsin inhibitor, and pregnancy

zone protein. The tPSA, that is typically measured, is made up of both the complexed and free forms (Long et. al, 2006).

It has been shown that the DRE has little effect on tPSA levels (Hoffman, 2010) and can be measured directly after the examination. However, it has been suggested that the cPSA is less sensitive to external influences compared to the tPSA, and, therefore, is a more reliable indicator for prostatic disorders.

Purpose of the Study

Since the PSA is currently the best screening tool available to date, it is important that the test be as accurate as possible. Many clinicians perform a DRE and request a PSA afterwards. The purpose of this paper is to perform a systematic review of the literature on the effect that the DRE has on the total and complexed PSA using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group (Guyatt et al., 2008).

METHOD

An extensive literature search was performed using Medline, Web of Science, Cochrane Systematic Reviews and CINAHL. These databases were accessed through the Pacific University Library system. The keywords searched were “manipulation”, “massage”, “PSA”, “prostate-specific antigen”, “DRE” and “digital rectal examination,” individually and in combination. The search was limited to human subjects, articles published in English since 2000. A total of 15 articles were identified on the original search. Duplicate and unrelated articles were eliminated and three articles remained. A reference search was done in the

Web of Science and one additional article was found that could be included in the study. The articles identified were observational studies that were included in the final review.

RESULTS

The first study reviewed was performed by Tarhan et al. (2005) and they set out to evaluate the effect a prostatic massage had on cPSA levels compared to tPSA and free PSA (fPSA) levels after various prostatic manipulations. The study included 51 men that had a mean age of 63.33 \pm 1.28 years. Of the 51 men in the analysis, 35 of the men had benign prostatic hyperplasia (BPH), seven had prostate cancer, and nine had prostatitis. The men had their prostate massaged for approximately one minute by the same examiner. The PSA serum samples were taken 30 minutes before and 30 minutes after the prostatic massage. According to their diagnosis, the serum values in ng/mL before and after manipulation are as follows for tPSA: BPH before 4.09 \pm 0.78, BPH after 8.02 \pm 1.33, prostate cancer before 18.21 \pm 6.64, prostate cancer after 19.91 \pm 6.62, prostatitis before 2.06 \pm 0.46, and prostatitis after 6.32 \pm 1.19. Similar results were then reported using the cPSA: BPH before 2.62 \pm 0.53, BPH after 2.80 \pm 0.53, prostate cancer before 12.52 \pm 3.68, prostate cancer after 12.11 \pm 3.53, prostatitis before 1.40 \pm 0.35, and prostatitis after 1.90 \pm 0.36. Tarhan et al. (2005) concluded that prostatic massage increased cPSA levels, but not to the extent tPSA and fPSA levels were increased.

The next study reviewed was performed by Long et al. (2006) and included 113 men in the study. They performed several forms of prostatic

manipulation in an effort to compare the effect the treatment has on cPSA and tPSA. The men received various forms of prostatic manipulation which included DREs, flexible cystoscopy, rigid cystoscopy, prostate biopsy and transurethral resection of the prostate. Of the 113 men in the study 34 had DREs. The DRE was performed in the left lateral position by the same clinician. The mean age of the men was 67 and their ages ranged from 29 to 87. Their ages were not broken out by the type of manipulation they had undergone. The PSA serum samples were taken 20 minutes before and after the DRE. The results were presented by how much the measurement changed using a paired t-test. The change in tPSA in ng/mL was 0.81 ± 0.84 and the change in cPSA was 0.63 ± 0.74 . The authors concluded that cPSA levels are less vulnerable to prostatic manipulation than are the tPSA levels.

Lynn et al. (2000) study was reviewed. They had 92 men in the study with a mean age of 68.6 years and they set out to collect data on the effects that various forms of prostatic manipulation has on cPSA levels. The men received different forms of prostatic manipulation that included prostatic biopsy, flexible cystoscopy and DRE. Of the 92 men, 16 were evaluated after a DRE. The DRE was performed in the left lateral position by the same investigator. The PSA serum samples were taken 30 minutes before and after the DRE. The tPSA data was presented which showed the change post DRE. The tPSA for before, after, and the change post DRE including the confidence intervals were 8.41 (0.74-16.07), 9.13 (0.89-17.38), and 0.72 (0.06-1.4), respectively. The cPSA for before, after, and the change were 5.95 (1.11-10.79), 5.98 (1.07-10.9), and 0.03

(-0.1-0.17) in that order. The authors concluded that prostatic manipulation results in minimal changes in cPSA levels.

The final study reviewed was the Lin et al. (2010) study that evaluated 160 males with a mean age of 68 years. They set out to determine how various forms of prostatic manipulation affect the tPSA and free-to-total prostate specific antigen (f/tPSA). There were a variety of prostatic manipulations which included DRE, urethral catheterization, rigid cystoscopy, prostate biopsy, transurethral resection of the prostate and suprapubic subcapsular prostatectomy. Of those participants, 23 underwent DRE for BPH. This study included data on tPSA and not cPSA. Serum PSA was gathered before the manipulation, at 24 hours and at 4 weeks. The tPSA, along with the confidence intervals, in ng/mL before, 24 hours after, and 4 weeks after were 1.96 (1.31-2.61), 1.97 (1.31-2.63), and 1.96 (1.30-2.62) respectively. The authors concluded that the DRE has minimal effects on tPSA levels.

DISCUSSION

Beginning at the age of 50 and based on clinician and patient preference, millions of men are evaluated for prostate cancer by having a DRE and tPSA. This is done earlier, if prostate cancer runs throughout the family, or if an individual is at high risk or has symptoms of poor prostate health. The tPSA is highly variable and unreliable and has a sensitivity and specificity of 20 to 40 percent (Fischbach & Dunning, 2009).

In the past, there has been speculation that any type of manipulation on the prostate can influence tPSA levels. Studies have shown that the DRE and

tPSA levels can be done in the same visit (Hoffman, 2010). However, there is some variation post manipulation and it would be better to ensure that a test that has such a low sensitivity and specificity already, be less influenced by external factors. A false positive test can result in an individual undergoing additional testing which may include referrals to urologists, additional blood testing and possible biopsies or other invasive procedures. Certainly this could lead to an exponential rise in the individuals' medical expenditures, but this could also lead to the person missing time and money due to lost work as well as burdening the individual with undue stress due the potential threat of prostate cancer becoming a reality rather than a possibility. Therefore, it is crucial to improve the reliability of the PSA test.

The complexed PSA is a subset of the total PSA and therefore, it will by definition change less numerically in relation to the total PSA. However, the percent change would be a more reliable indicator as how much it would change after the prostate had been manipulated and Lynn et al. (2000) and Tarhan et al. (2005) demonstrated that the cPSA in relation to tPSA had a percentage change of 0.50 and 6.43 compared to 7.89 and 49.00, respectively. Long et al. (2006) also showed a smaller mean change of cPSA in relation to tPSA, but the results were highly variable. Lin et al. (2010) showed that the tPSA undergoes minimal change in tPSA 24 hours after a DRE, but the cPSA was not evaluated. All this information combined would suggest that the tPSA is not significantly affected by the DRE and the blood tests could be done after the clinical examination. However, due to the inherent unreliability of the tPSA test, using the cPSA

instead would only improve the reliability of the results leading to fewer false positives. In summary, the cPSA is a more reliable clinical indicator of measuring prostate health than the tPSA.

Study Limitations

The Lin et al. (2010) study had 23 individuals which is similar in total to the other three studies. The urologists were instructed to perform a regular DRE without vigorous prostatic massage so there was no dose-response curve. It was difficult to determine if their age had any effect on the measurements. The study had a total of 160 individuals in it that had various procedures including the 23 that had a DRE. The age range specified for the study was from 50 to 85 with a mean age of 68 years old. The ages were not broken out by who had what procedure so it is not evident if age is a factor in how tPSA responds to DRE manipulation. The conclusion of the study was that DRE manipulation resulted in no tPSA changes at 24 hours and at one week after a standard DRE was performed.

The Long et al. (2006) study had 34 participants. These individuals were all examined by the same clinician, but no specific instructions were given to the clinician so it was assumed it was a standard DRE and, therefore, no dose response curve was evaluated. As with the other study there was a wide range of ages from 29 to 87 years of age. Since screening for high risk individuals begins at 40 it is difficult to determine if age skewed the results. This study also included multiple procedures and actually had 113 patients included in the study of whom 34 of the participants were subject to a DRE. As a result, it is uncertain

what factor, age played in the variation of tPSA and cPSA if any. The results were also displayed showing a mean change rather than the raw score. This made it impossible to determine the actual percentage change so it could only be said that, without having all the data, the cPSA showed a smaller variation than tPSA. Their conclusion was that cPSA is less prone to variations and is a more reliable marker and should be considered to replace tPSA.

Tarhan et al. (2005) had 51 males that contributed to the study. These men were given a prostatic massage for approximately one minute by the same investigator. Since all the men received the one minute massage there could be no comparison made according to a dose response. The individual ages, according the condition being treated, had been established in this study unlike the others. They were then compared, before and after, according to their condition as well as a summarized total. This study displayed the data in a very organized format and was very straight forward, but it is recognized that due to the sample size of the study and limit to one variable in terms of length of massage, the quality of the evidence remains low. For instance, it would have been helpful to see a standard DRE versus a one minute prostatic massage. The overall result of the study is that prostatic massage increased the cPSA, but less than tSPA.

Finally, Lynn et al. (2000) had 16 participants. The DRE was carried out by the same examiner. As with the other studies, there is no explanation as to how long it took to perform a DRE so no dose response curve could be evaluated. This study actually had 92 members in it of which 16 received a DRE

while others underwent other procedures. The study had a mean age of 68.6 years with ranges from 66.6 to 70.5 years of age. Although the age ranges were fairly close, it would have been helpful to see the ages broken out by the type of procedure they underwent. The conclusion of the study is that is unclear why cPSA levels remain unchanged after prostatic manipulation.

GRADE Evaluation

The GRADE system is a tool aimed at using a sensible approach to grading the quality of evidence as well as the strength of a recommendation. There are four grades in the grade system that include high, moderate, low, and very low. A high grade means that “further research is highly unlikely to change the confidence in the estimate of effect” whereas a moderate grade denotes that “additional research is likely to have an important impact on the confidence in the estimate of effect” (Guyatt et al., 2008, p.926). A low grade implies that “further research is very likely to have an important impact on the confidence of the estimate and is likely to change it” while a very low grade means “signifies the effect is uncertain” (Guyatt et al., 2008, p.926). All four outcomes used, started and ended with a grade of low because they were observational based studies that did not merit upgrading based on large magnitude of effect, dose-response, and elimination of confounders.

Conclusions

In summary, the effect the DRE has on cPSA is minimal in comparison to the tPSA (Appendix B-Figure 1). All four outcomes were given a low GRADE rating and a low grade using the GRADE system means that “further research is

very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate” (Guyatt et al., 2008, p.926). Additional well designed studies need to be performed to evaluate cPSA replacing tPSA as the standard marker to determine prostate health. This would involve gathering large amounts of baseline cPSA data to determine what ranges the test measurement would be, to be considered normal and abnormal. Furthermore, it would be beneficial if the individual studies included large sample sizes with varying prostatic manipulation times using a randomized double blinded fashion to determine how long the prostate is manipulated, has on the effect of the cPSA. Additionally, it has been shown that ejaculation may cause an increase in the tPSA levels by up to 0.8 ng/mL for up to 48 hours and all of the studies failed to include questioning their participants about their sexual history (Hoffman, 2010). It would have also been beneficial to know the habits of their participants such as bicycling, caffeine and alcohol intake, and smoking status. The data may not be changed by including those questions to future participants, however it ensures that additional potential confounders have been accounted for or at least taken into consideration. It has been shown that the DRE has little effect on tPSA levels (Hoffman, 2010), nonetheless it would be beneficial to rule out that the DRE may affect the tPSA or cPSA levels based on how much manipulation is done to the prostate prior to running the test. This would be very important clinically as the investigator may feel an abnormality and spend more time or get another opinion of a colleague and unknowingly elevate the results. Tarhan et al. (2005) study manipulated the prostate for one minute and Lynn et al. (2000)

performed a standard DRE in which they did not describe the length of time the prostate was manipulated. This could explain the disparity in figure 1 (Appendix B).

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APPENDIXES

APPENDIX A
Table 1: GRADE Table

Comparison	Outcome	Quantity and type of evidence	Findings	Starting grade	Increase GRADE			Grade of Evidence for Outcome	Overall GRADE of Evidence
					Large Magnitude	Dose-Response	Confounders		
Elevation in serum PSA post manipulation	tPSA	4 observational studies	Positive association	Low	0	0	0	Low	Low
	cPSA	3 observational studies	Positive association	Low	0	0	0	Low	

APPENDIX B

Figure 1: Percent change in PSA levels

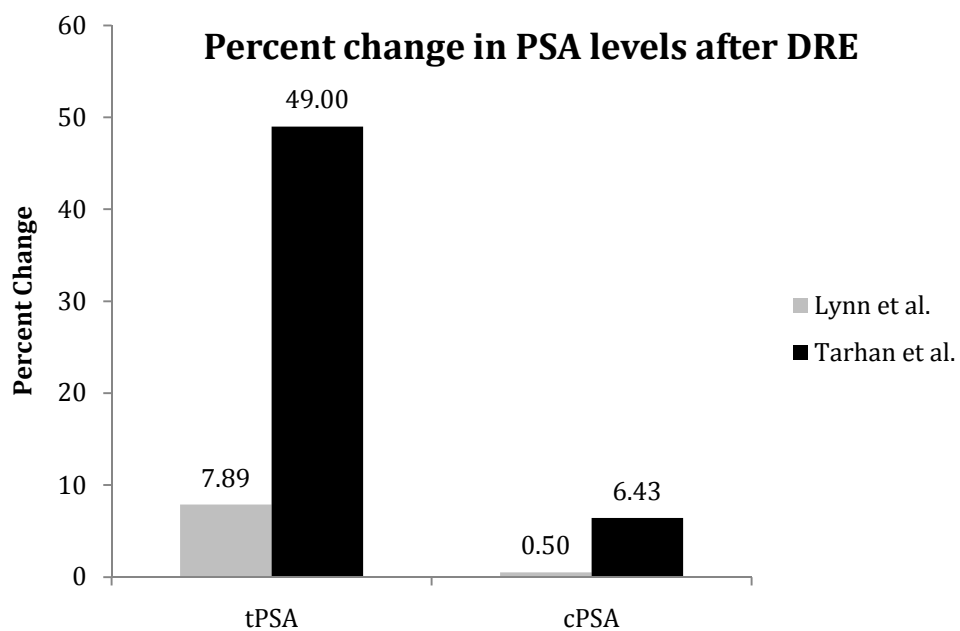


Figure 1: Percent change in PSA levels approximately 30 minutes post Digital Rectal Examination. Figure recreated using data courtesy of Lynn et al. and Tarhan et al.